Pathogenesis of Herpes Simplex Labialis: Experimental Induction of Lesions with UV Light

SPOTSWOOD L. SPRUANCE

Divisions of Infectious Diseases and Dermatology, Department of Medicine, and Center for Infectious Diseases, Diagnostic Microbiology and Immunology, University of Utah School of Medicine, Salt Lake City, Utah 84132

To develop a model system of herpes simplex labialis which would enable the study of patients before lesion onset, five patients were exposed to various doses of UV light from a sunlamp at their usual site of lesions. Six of 10 treatments resulted in the development of herpes labialis. Three of four treatments with the highest exposure levels led to large, vesicular, virus culture-positive sores. Side effects from sunlamp exposure were minimal.

Despite impressive advances in the understanding of human herpes simplex virus (HSV) infections, much remains to be learned about latency, trigger factors which induce recurrent infection, and means of therapeutic intervention. Experimental animal models such as primary and recurrent genital HSV type 2 infection in guinea pigs (11) and recurrent HSV type 1 infection in the ears of hairless mice (5) are important means for further study. Human experimentation is critical for biologic and therapeutic questions that may be specific for the human host.

high risk for recurrent disease has provided insights, but lesion development in these subjects is unpredictable (2, 7). Prospective studies of patients experiencing known trigger factors such as fever (3) and trigeminal nerve surgery (6) also have been useful, but the coexistence of other illnesses and the restricted availability of this kind of study subject are limiting factors.

Herpes labialis is known to be precipitated by sun exposure in susceptible individuals, although the mechanism by which this occurs is unknown. In 1975, Wheeler (13) showed

TABLE 1. Time of onset and severity of herpes simplex labialis induced by exposure to UV light

Patient no.	Date	Sunlamp dose (MED)	Clinical outcome				
			No. of lesions induced	Interval between exposure and lesion onset (h)[a]	Maximum lesion stage[b]	Lesion size (mm^2)	Virus culture result
1	2/14	4	2	23	Papule	4	Negative
				67	Vesicle	24	Positive
	3/14	4	0				
	4/18	5	0				
2	2/17	4	0				
	4/22	5	1	94	Vesicle	45	Positive
3	3/8	4	1	60	Erythema		Negative
4	4/6	4	2	41	Vesicle	8	Negative
				75	Vesicle	8	Negative
5	4/5	4	0				
	4/29	5	1	67	Vesicle	50	Positive
	7/31	6	1	58	Vesicle	180	Positive[c]

[a] Lesion onset was defined as the first physical evidence of a lesion.
[b] Most severe lesion stage by the criterion: vesicle > papule > erythema.
[c] Lesion culture was not done, but saliva culture was positive.

Several studies of recurrent herpes simplex labialis have been conducted by serial observations of untreated subjects with early lesions (1, 9). Although valuable information can be derived from natural history studies, these protocols fail to provide information about the period before a recurrence. Prospective daily monitoring of small numbers of subjects at

that recurrent cutaneous HSV type 2 infection on the lower extremities of three patients could be reactivated experimentally with UV light from an artificial source. It seemed likely that herpes labialis could be reactivated in a similar fashion in a controlled setting with a sunlamp. Such a procedure would be potentially valuable as a model to study the
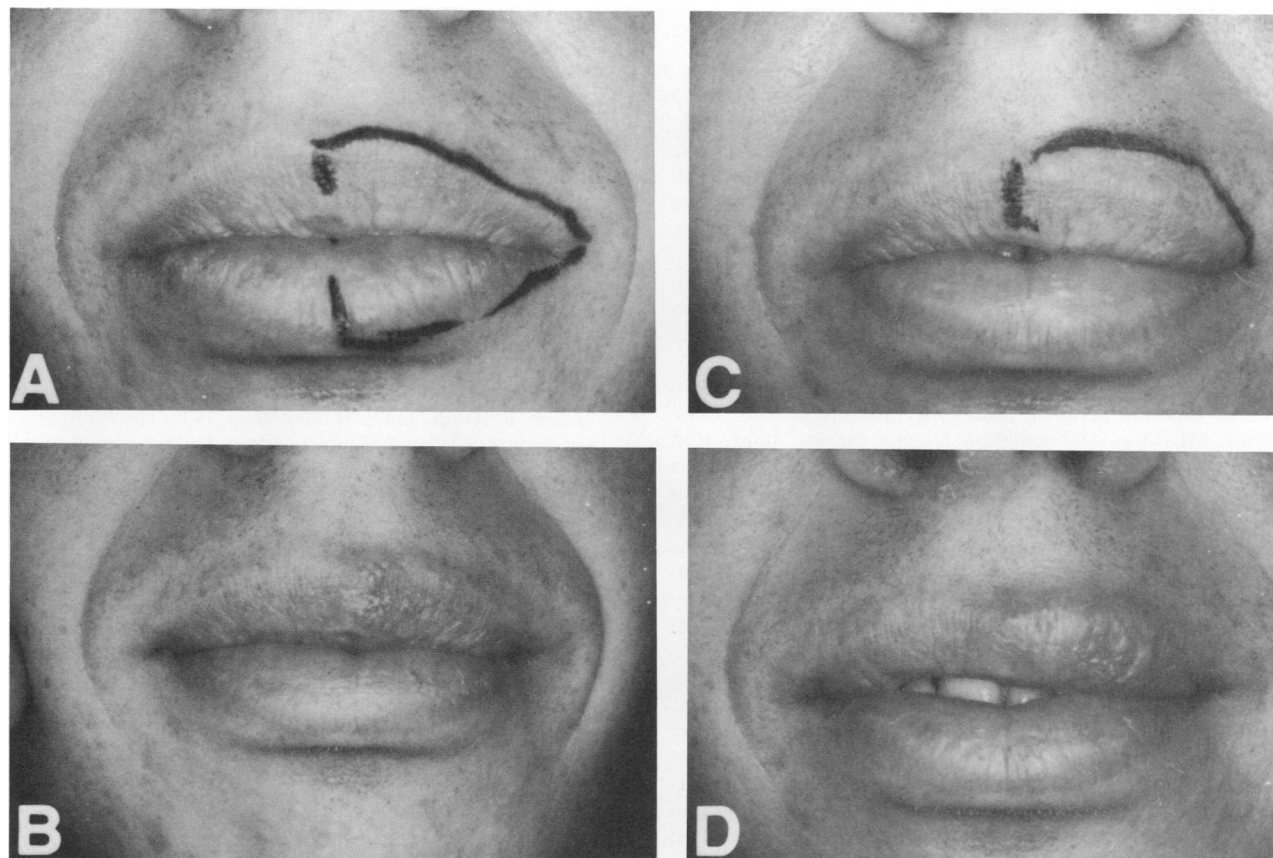
FIG. 1. (A) Patient 5 was exposed on the left upper and lower lips to 5 MED of UV light. The remainder of the face was protected with a sunscreen. The usual site of recurrence is the left upper lip. (B) Subsequent lesion formation within the area of irradiation. (C) The patient was exposed a second time to 6 MED of light on the left upper lip only. (D) Subsequent lesion.

pathogenesis and treatment of the disease, with the advantage to the investigator of access to the patient immediately before lesion onset.

MATERIALS AND METHODS

The records of former clinic patients were examined to identify persons with a history of herpes labialis provoked by exposure to the sun. Individuals under 18 years of age were excluded, as were those taking photosensitizing drugs. This study was institutional review board-approved, and all patients signed a document of informed consent.

The light source was a standard retail cosmetic sunlamp (GTE Sylvania, Inc., Manchester, N.H.). For each subject, the minimal erythema dose (MED) was determined by exposing areas (2 × 2 cm) of the ventral forearm skin for 1 to 7 min with the sunlamp at a distance of 75 cm. One MED was defined for each patient as the minimal duration of sunlamp exposure in minutes that produced erythema under these experimental conditions.

After the establishment of the MED for each patient, subjects were exposed on the face to a dose of 4 MED. Patients wore protective goggles. All areas of the face except the lips and immediate perioral skin were protected with a 5% formulation of p-aminobenzoic acid (Eclipse SPF15; Allergan Pharmaceutical, Irvine, Calif.). Selected patients had only the lips or a portion of the lips exposed, according to the usual location of their recurrences. Patients not responding to 4 MED were treated later with 5 or 6 MED. A

month elapsed between treatments of patients who had multiple exposures.

Lesions were sampled with a Dacron-tipped swab and assayed for HSV by observation of typical cytopathic effect in Vero cells. The saliva of one patient was examined for HSV by techniques which have been reported in detail elsewhere (7).

RESULTS

Five patients received a total of 10 UV light exposures and subsequently were followed carefully for 5 days to detect the development of herpes labialis (Table 1). Six of the 10 treatments resulted in the development of a lesion. The interval between sunlamp treatment and lesion onset (first physical sign) was 23 to 94 h (mean, 61 h). Four of eight lesions sampled for virus identification were positive for HSV (one patient had a positive saliva culture).

Three of six treatments with an MED of 4 resulted in lesions, but most of these were small and virus culture negative. Conversely, three of four treatments with 5 or 6 MED led to large, vesicular lesions, all of which were virus culture positive.

The induced lesions occurred within the area of sunlamp exposure. One lesion (in patient 2) developed at the border between exposed and shielded skin. Figure 1 shows lesions induced on two occasions by 5 and 6 MED in patient 5. The location of the lesions closely corresponded to the area of irradiation.

Symptoms attributable to the sunlamp treatment were

minimal. Patients reported mild erythema and discomfort for 1 to 2 days at the site of exposure.

DISCUSSION

These data indicate that herpes labialis can be induced in susceptible subjects with UV light from a retail cosmetic sunlamp. The frequency of induced lesions was dose related. Exposures of 5 to 6 MED resulted in virus culture-positive vesicular lesions on three of four occasions. The procedure was well tolerated, because light exposure was restricted to the usual lesion site and the dose was carefully regulated. This experimental protocol shows promise as a model system for the study of the mechanism and treatment of recurrent cutaneous HSV infection.

There are two unresolved theories concerning the mechanism of development of recurrent mucocutaneous HSV infection (4). One, the ganglion trigger theory, holds that new viral synthesis occurs in the sensory ganglia after a stimulating event, whereupon virus travels retrograde down sensory axons and initiates infection in the epidermal cells. The other, the skin trigger theory, holds that virus is continuously shed from neuronal endings and lesions develop when the susceptibility of the skin is sufficiently permissive for the development of a clinically apparent infection.

Anecdotal clinical impressions indicate that lesions develop 2 to 3 days after sunburn, but this information is difficult to evaluate from a mechanistic perspective because the stimulus from natural light exposure often occurs over a prolonged or intermittent period of time. The present experimental data show that herpes labialis lesions occur at a variable interval of 23 to 94 h after a brief, circumscribed photic stimulus to the skin. This pattern of lesion development is most compatible with the skin trigger hypothesis. The different times of lesion onset, especially of the earliest lesions, could be attributed to a lesion-promoting effect by photic skin damage on ongoing subclinical epidermal cell infections at different stages of development. A point source pattern of lesion occurrences would have favored the ganglion trigger theory. The model offers a further opportunity for pursuit of these questions by combining light exposure and systemic antiviral therapy. For example, if the skin trigger hypothesis is true and early lesions (after light exposure) actually had their onset before the light stimulus, then pretreatment of subjects with oral acyclovir should eliminate early lesions and narrow the temporal distribution of lesion occurrence.

A variety of other questions concerning disease pathogenesis might also be pursued with the model. For example, ingestion of lysine, corticosteroids, or inhibitors of prostaglandin synthesis after UV light exposure might help to elucidate the role of amino acid metabolism, immunologic factors, or prostaglandins in the development of a recurrence (4, 12).

The rapid natural evolution of herpes labialis and the great variability in disease severity requires patient-initiated treatment protocols and many subjects for the proper evaluation of new therapeutic agents (8, 10). These large studies are expensive and time consuming. Alternatively, the use of experimentally light-exposed subjects prophylactically treated with an antiviral drug or placebo could reduce the number of subjects required and facilitate a rapid and relatively inexpensive determination to screen a formulation for clinical merit. Such studies could serve as the basis for larger field trials of persons with naturally recurrent disease.

LITERATURE CITED

1. **Bader, C., C. S. Crumpacker, L. E. Schnipper, B. Ransil, J. E. Clark, K. Arndt, and I. M. Freedberg.** 1978. The natural history of recurrent facial-oral infection with herpes simplex virus. J. Infect. Dis. **138**:897–905.
2. **Douglas, R. G., and R. B. Couch.** 1969. A prospective study of chronic herpes simplex virus infection and recurrent herpes labialis in humans. J. Immunol. **104**:289–295.
3. **Greenberg, M. S., V. J. Brightman, and I. I. Ship.** 1969. Clinical and laboratory differentiation of recurrent intraoral herpes simplex virus infections following fever. J. Dent. Res. **48**:385–391.
4. **Hill, T. J., and W. A. Blyth.** 1976. An alternative theory of herpes simplex recurrence and a possible role for prostaglandins. Lancet **i**:397–399.
5. **Hill, T. J., H. J. Field, and W. A. Blyth.** 1975. Acute and recurrent infection with herpes simplex virus in the mouse—a model for studying latency and recurrent disease. J. Gen. Virol. **28**:341–353.
6. **Pazin, G. J., M. Ho, and P. J. Jannetta.** 1978. Reactivation of herpes simplex virus after decompression of the trigeminal nerve root. J. Infect. Dis. **138**:405–409.
7. **Spruance, S. L.** 1984. Pathogenesis of herpes simplex labialis: excretion of virus in the oral cavity. J. Clin. Microbiol. **19**:675–679.
8. **Spruance, S. L., C. S. Crumpacker, L. E. Schnipper, E. R. Kern, S. Marlowe, K. A. Arndt, and J. C. Overall, Jr.** 1984. Early, patient-initiated treatment of herpes labialis with topical 10% acyclovir. Antimicrob. Agents Chemother. **25**:553–555.
9. **Spruance, S. L., J. C. Overall, Jr., E. R. Kern, G. G. Krueger, V. Pliam, and W. Miller.** 1977. The natural history of recurrent herpes simplex labialis. Implications for antiviral therapy. N. Engl. J. Med. **297**:69–75.
10. **Spruance, S. L., and G. Wenerstrom.** 1984. Pathogenesis of herpes simplex labialis. IV. Evolution of lesions during the first 24 hours after onset and implications for antiviral treatment. Oral Surg. Oral Med. Oral Pathol. **58**:667–671.
11. **Stanberry, L. R., E. R. Kern, J. R. Richards, T. M. Abbott, and J. C. Overall, Jr.** 1982. Genital herpes in guinea pigs: pathogenesis of the primary infection and description of recurrent disease. J. Infect. Dis. **146**:397–404.
12. **Tankersley, R. W., Jr.** 1964. Amino acid requirements of herpes simplex virus in human cells. J. Bacteriol. **87**:609–613.
13. **Wheeler, C. E., Jr.** 1975. Pathogenesis of recurrent herpes simplex infections. J. Invest. Dermatol. **65**:341–346.